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Intraoperative radiation therapy with electrons in breast cancer conservative treatment: Our experience

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ABSTRACT

Radiotherapy plays a central role in the local control of breast cancer following conservative surgery, representing the standard treatment for patients undergoing quadrantectomy or lumpectomy and consisting in 5 or 6 weeks of treatment with a total dose of 45–50 Gy.

In the last ten years new trends in radiation therapy have been developing with a new planning of duration and extension of breast tissue to irradiate.

Moreover some authors presented the idea of combining the use of intraoperatory radiotherapy with the partial breast irradiation, with the aim of irradiate the breast in a single session during breast conserving surgery.

From September 2009 to July 2010 we prospectively enrolled 13 patients to undergo electron beam intraoperative radiotherapy after breast conservative treatment for early breast cancer.

At a mean follow-up of 46 months no local recurrences have been described and no patients presented distant metastasis or died for any cause. 6 patients (46.2%) presented complications, as fibrosis and liponecrosis.

Our results suggest that electron beam intraoperative radiotherapy in the conservative treatment of breast cancer could be considered a suitable option for low risk patients, even if our sample is very small and we need longer follow-up to draw conclusive results.

1. Introduction

Breast cancer represents 10.4% of all cancers in women, being the second most common non-cutaneous cancer after lung cancer and the fifth cause of death [1].

Every year in Italy, around 40,000 women have a diagnosis of breast cancer and 60% of all breast cancers are diagnosed in early stage, thanks to the widespread use of mammographic screening [2–4].

Therefore an appropriate management of early breast cancer results mandatory.

Since Veronesi's Milan trial in 1981 [5] and many other international phase III trials [6–10] confirmed the central role of radiotherapy in the local control of breast cancer following conservative surgery, the standard treatment for patients undergoing quadrantectomy or lumpectomy for breast cancer is represented by 5 or 6 weeks of radiotherapy with a total dose of 45–50 Gy (1.8–2 Gy for fraction).

All studies showed low short-term complications rates related to radiotherapy even when conducted before the introduction of modern radiotherapic techniques with tridimensional planning, intensity-modulation and gated-radiotherapy for left breast cancers.

Adjuvant radiotherapy not only reduces local recurrences but determines a better overall survival [11,12].

On the other hand, many women candidates to radiotherapy after breast conservative surgery do not indeed undergo radiation therapy or prefer a radical surgery because of logistic or job-related difficulties in attending 6 weeks of therapy [13–17].

From 10 to 80% of all women undergoing breast conservative surgery really perform radiotherapy as an adjuvant treatment [18,19].

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Moreover in the last ten years new trends in radiation therapy have been developing with a new planning of duration of the treatment and extension of breast tissue to irradiate.

According to recent studies, the total duration of radiation treatment could be reduced to a half or a third, following different fractioning with an augmentation of the single dose for application and reduction of the fractions [20–22].

Moreover, according to the evidence that 85% of local recurrences present at the level of the same quadrant of the index cancer, partial breast irradiation (PBI) has being widely applicated, reducing the application fields from the whole breast to the area of the cancer.

Since about ten years some authors presented the idea of combining the use of intraoperatory radiotherapy (that is radiation therapy delivered during the surgery in the operating theatre) with the partial breast irradiation, with the aim of irradiate the breast in a single session during breast conserving surgery.

Electron beam intraoperative radiotherapy releases a single dose of radiation for a duration of 3 min directly on the cancer field following quadrantectomy or lumpectomy using a linear accelerator directly in the operation theatre, completely equivalent to the entire dose of an external beam six-week fractionated radiotherapy.

2. Material and methods

After obtaining our institution's ethical committee approval, from September 2009 to July 2010 we prospectively enrolled 13 patients to undergo electron beam intraoperative radiotherapy after breast conservative treatment for early breast cancer.

We enrolled our patients according to the following inclusion criteria: post-menopausal women younger than 75 (menopause was defined as: amenorrhea for more than 6 months if older than 50; amenorrhea for more than 12 months if younger than 50; bilateral oophorectomy; if submitted to hysterectomy: menopause if older than 50, serological confirmation if younger than 50); cytological diagnosis of breast invasive ductal carcinoma; unicentricity and unifocality of the disease (at magnetic resonance imaging); no evidence of distant metastasis (at bone scintigraphy and total body CT scan); ultrasonographic diameter of the lesion less than 2.5 cm; negative sentinel lymph node biopsy.

Detailed information about the study was given to each patient and written informed consent form was signed by each woman enrolled.

Patients have been excluded from our study if: cytological diagnosis of a different breast carcinoma histotype; skin infiltrating cancer; cancer at the level of the breast axillary tail; diseases that contraindicate radiation therapy, as connective tissue diseases, previous thoracic irradiation, etc.)

2.1. Surgical and radiotherapic technique

All patients underwent quadrantectomy and sentinel lymph node biopsy (SLNB). SLNB was performed through the same surgical access used for the tumor excision for cancers localized at the upper outer quadrant and through a separate skin incision for other localizations. Sentinel lymph node was histologically examined intraoperatively. If positive for metastatic cells, the patient would not be submitted to intraoperative radiotherapy and excluded from the study. Surgical excision margins around the cancer were always at least 1 cm. Margins never resulted infiltrated at definitive histology and the definitive histological examination of the sentinel lymph node always confirmed the intraoperative diagnosis.

Cancer grading was evaluated according to Elston and Ellis score [23] and peri-tumoral vascular invasion according to Rosen [24]. Immunohistochemical evaluation of estrogen and progesterone receptors, Ki-67 (with monoclonal antibody MIB 1) and c-erb B2 expression was assessed for each patient.

After removing the cancer with adequate surgical margins, residual glandular tissue was mobilized from the fascia of the pectoralis major muscle for at least 5–10 cm around the tumor bed in order to better approximate the breast parenchyma to the center of the incision and expose the residual gland to the radiation beam. Superficial margin of the breast parenchyma was mobilized for 4–5 cm in every direction around the tumor bed.

In order to minimize the dose of radiation delivered to the thoracic wall and to guarantee the release of the entire radiation dose to the gland, a dedicated lead 5 mm thick disk (available in different diameters (4, 5, 6, 8 and 10 cm)) was positioned between the gland and pectoralis major muscle. In order to guarantee an optimal chest wall protection, the disk must be larger than the area to irradiate.

The gland was then temporarily approximate to better expose the exact parenchyma to the radiation beam, avoiding dishomogeneity in the target volume shape, after positioning the protection disk under the gland.

The energy of the electron beam was chosen in relation to the target volume thickness.

The isolation of the skin from the collimator results fundamental in order to avoid skin irradiation. If the skin would come into direct contact with the polymethyl methacrylate (Perspex; Hitesys SpA, Aprilia, Italy) collimator, its margins would receive 5% of the total dose. A dedicated device was used to completely separate the skin from the radiation area, consisting of a metallic ring of variable diameter connected to small nontraumatic metallic hooks. Alternatively the skin margins were protected with wet sterile gauzes inserted between the skin and the collimator, creating a barrier able to absorb the low-energy electrons scattered around the collimator edge.

After these procedures, the sterile collimator of the linear accelerator (LINAC) was placed in the right position in order to guarantee the complete coverage of the target volume.

The glandular portion to be irradiated (clinical target volume) is an area of 4–6 cm of diameter around the tumor bed but, according to the breast volume and the technical possibility of mobilizing the residual gland, it is possible to irradiate up to 10 cm of glandular parenchyma.

The diameter of the collimator is chosen according to the diameter of the area to irradiate in order to cover the entire tumor bed and a safety margin (at least 2 cm in all directions).

The applicator was then placed into direct contact with the breast gland, moving the LINAC through a dedicated remote controller.

It is important to avoid herniation of part of the gland into the collimator resulting in an increase of the dose to the superficial part of the target (with this aim a perspex disk was positioned over the gland to irradiate and was adapted to the terminal part of the applicator).

After positioning the applicator, 3 mobile barriers were positioned around the operating table (lead thickness 1.5 cm, height 150 cm and width 100 cm) and under the table (mobile trolley with a lead portion of 1.5 cm in thickness) to guarantee a good shielding of x-rays scattered by the patient.

All personel left the operating theatre and irradiation was started through the control panel.

The irradiation was performed in two consecutive steps, in each of which half of the dose was delivered. An in-vivo dosimetry was performed with a dedicated dosimeter with an electronic device placed just under the perspex disk at the terminal surface of the applicator in order to control the dose released to the patient.

The total dose was of 21 Gy, prescribed at the 90% isodose, through four energy levels of electrons (3, 5, 7 and 9 MeV).

The entire radiation procedure was completed in 2–4 min.

After delivering the radiation dose, the applicator was removed and the LINAC moved out of the operating table. The stitches used to approximate the breast parenchyma were partially or completely removed in order to eliminate the protection disk. The parenchyma was then reapproximated and the skin incision sutured with non-absorbable material.

3. Results

Patients' mean age was 59 years (range 50–72). All women were affected by monofocal breast invasive ductal carcinoma (monofocality at magnetic resonance imaging and cytological diagnosis of breast carcinoma) less than 2.5 cm in diameter (mean diameter 1.56 cm, range 0.8–2.3 cm).

Adjuvant medical treatments were prescribed according to protocols in use in the Oncology Department of our Hospital. 8 patients (61.5%) received hormone therapy only, 1 (7.7%) chemotherapy only, 4 (30.8%) both adjuvant treatments. 5 patients also underwent immunotherapy with Trastuzumab.

Follow-up was performed according to the study protocol: after 15 days from the procedure all patients were evaluated by a multidisciplinary team (composed by an oncologist, a radiotherapist and a surgeon) in order to define the adjuvant treatments to perform and to first clinically evaluate the area submitted to IORT.

All patient were then directed to oncological, radiotherapic and surgical follow-up in order to evaluate the loco-regional conditions in terms of: short-term and long-term complications, cosmetic results and oncological outcomes (local recurrence and overall survival).

Follow-up visits were performed at one month from the procedure and then at 3, 6 and 12 months; after the first year all women have been followed-up each 6 months until the 5th year.

At December 2013 mean follow-up was 46 months (range 41–51 months).

No patients were lost to follow-up.

All patients at follow-up visits have been evaluated using the RTOG/EORTC scale to detect short- and long-term complications [25].

6 patients (46.2%) presented complications. 1 patient (7.7%) presented hematoma in the immediate postoperative period. The same patient then presented severe fibrosis. Two patients (15.4%) presented moderate fibrosis. Fibrosis presentation was progressive in the months after the procedure, reaching the acme at one year after the procedure and then remaining stable. These 3 patients presented a slight skin retraction, affecting the cosmetic result. 3 patients (23.1%) presented liponecrosis from the fourth-fifth postoperative day to the tenth-eleventh day. We found this complication in women with large and adipose breasts.

Asymptomatic findings of liponecrosis at surveillance mammography were found in 4 patients (30.8%), while ultrasonographical images of non univocal interpretation have been found in 3 patients (23.1%). These findings lead to second-level procedures as ultrasound-guided fine-needle aspiration cytology (US-FNAC) to confirm the nature of the lesion (confirmed to be benign).

No local recurrences have been described at the last follow up of December 2013 and no patients presented distant metastasis or died for any cause.

4. Discussion

Our results suggest that electron beam intraoperative radiotherapy in the conservative treatment of breast cancer could be considered a suitable option for low risk patients, even if our sample is very small and we need longer follow-up to draw conclusive results.

Local control of disease through breast conserving surgery and intraoperative radiotherapy remains to be defined and long-term complications, as severe fibrosis or liponecrosis could compromise cosmetic results, leading to reduced satisfaction levels and worst quality of life for breast cancer patients. Moreover long-term complications could impact on mammographic and ultrasonographic postoperative surveillance, with higher need of second-level exams due to suspect findings with obvious negative psychologic and economic implications.

Many international scientific societies, as the German Society for Radiation Oncology (DEGRO) do not consider IORT as a gold standard as adjuvant treatment for breast cancer.

Therefore IORT should remain a treatment to be used only in experimental studies and research projects.

DEGRO encourages further studies investigating IORT and other partial breast irradiation methods as potentially useful options in selected groups of patients with a well defined low-risk profile [26–30].

In contrast with these considerations, the American Society for Therapeutic Radiology and Oncology (ASTRO) [31] and the European Society for Therapeutic Radiology and Oncology (ESTRO) [31–33] published recommendations for clinical practice in guiding the selection of patients for partial breast irradiation outside from clinical trials. These indications have been criticized by the American Scientific Community [34] and have not been adopted by NCCN (National Comprehensive Cancer Network) [35].

ASTRO defines three groups for the use of patients for partial breast irradiation (PBI): "suitable", "to use with caution", "unsuitable" [34].

PBI is considered to be acceptable outside from a clinical trial only for "suitable" patients, represented by patients older than 60 years, with negative lymph nodes, T1 cancers, estrogen receptors positive, no lymphovascular invasion, surgical margins wider than 2 mm and no multicentricity.

Recently published data from the group of Orecchia [36] showed that intraoperative radiotherapy with electrons resulted in significantly higher local recurrence than did conventional postoperative external radiotherapy after 5 years of follow-up suggesting that intraoperative radiotherapy with electrons should be restricted to suitable patients only, once characteristics defining suitability have been defined.

In conclusion whole breast irradiation as adjuvant therapy following breast conservative surgery remains the gold standard, basing on well defined results in terms of local control of disease, acceptable cosmetic results and low toxicity.

The use of a new technique of partial breast irradiation as standard adjuvant treatment after or during breast conserving surgery will be possible only if this new technique will be equal or better than whole breast irradiation in terms of efficacy, impact on quality of life and costs.

Ethical approval

None.

Conflict of interest

The Authors have no conflict of interest or any financial support.

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Author contribution

Nicola Rocco: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Corrado Rispoli: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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Bruno Amato: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Antonello Accurso: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

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